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Stereoselective Total Synthesis and Absolute Configuration of the Natural Decanolides (−)-Microcarpalide and (+)-Lethaloxin. Identity of (+)-Lethaloxin and (+)-Pinolidoxin

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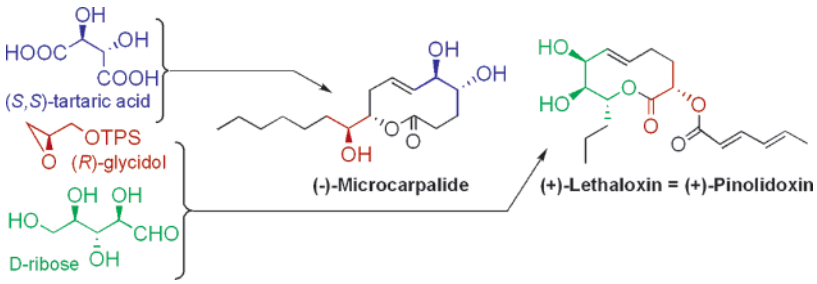
Received June 30, 2005



Convergent, stereoselective syntheses of the pharmacologically active, naturally occurring lactones (−)-microcarpalide and (+)-lethaloxin have been achieved from the commercially available, chiral reagents (*R*)-glycidol, (*S,S*)-tartaric acid, and D-ribose as the starting materials. These syntheses have further served to establish the hitherto unknown absolute configuration of (+)-lethaloxin and to show its identity with (+)-pinolidoxin.

Introduction

The generic name decanolides encompasses a relatively small class of naturally occurring 10-membered lactones of polyketide origin isolated in most cases from various species of fungi. Many of these lactones have been found to display pharmacologically interesting features, such as antibacterial, antitumoral, or hypolipidemic properties.[1] Two of these fungal decanolides are microcarpalide (**1**)[2] and lethaloxin (**2**).[3] Their structures and relative configurations (Figure 1) were determined with the aid of spectroscopic methods. The absolute configuration of **1**, depicted in the figure, was assigned by means of the exciton chirality method,[2] whereas that of **2** still remains unknown.

Microcarpalide **1** was isolated from an as yet unidentified endophytic fungus[4] growing on the bark of the tropical tree *Ficus microcarpa* L. While weakly cytotoxic to mammalian cells, the compound acts as a strong microfilament disrupting agent.[2] These properties make **1** a potential lead structure for the development of new anticancer drugs and, consequently, an attractive target for synthetic studies. Lethaloxin **2** was isolated from a strain of the fungus *Mycosphaerella lethalis*.[3] Like **1**, it is a trihydroxy 10-membered lactone, but one of its hydroxyl groups is esterified with sorbic acid. The first total synthesis of **1** was published by us in 2002.[5] In subsequent years, syntheses of either the natural product or its non-natural enantiomer were reported in the

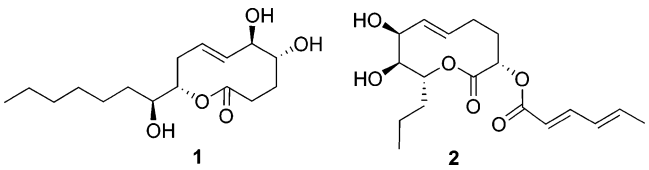


FIGURE 1. Structures of microcarpalide (**1**) and lethaloxin (**2**).

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(1) For a review on synthetic, biosynthetic, and pharmacological aspects of decanolides, see: Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep*. **1996**, *13*, 365−375.

(2) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. *Org. Lett.* **2001**, *3*, 3479−3481.

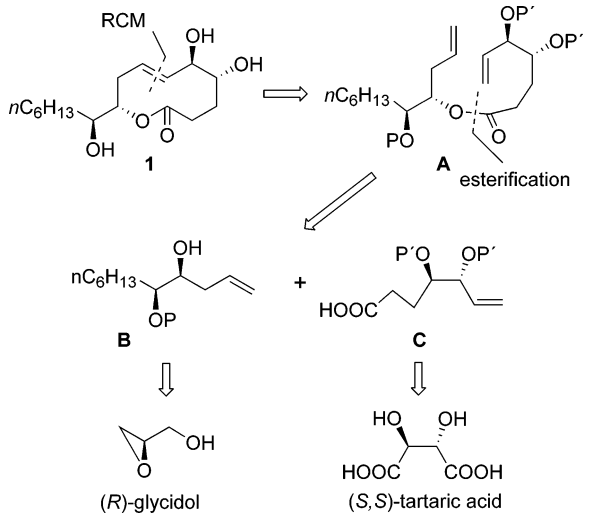
(3) Arnone, A.; Assante, G.; Montorsi, M.; Nasini, G.; Ragg, E. *Gazz. Chim. Ital*. **1993**, *123*, 71−73. The structure of lethaloxin depicted in this paper corresponds to the enantiomer of **2**.

(4) For a review on secondary metabolites isolated from this type of organism, see: Tan, R.-X.; Zou, W.-H. *Nat. Prod. Rep*. **2001**, *18*, 448−459.

(5) Murga, J.; Falomir, E.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett*. **2002**, *4*, 3447−3449.

10.1021/jo051353p CCC: $30.25
Published on Web 10/27/2005

SCHEME 1. Retrosynthetic Plan for Microcarpalide (1)



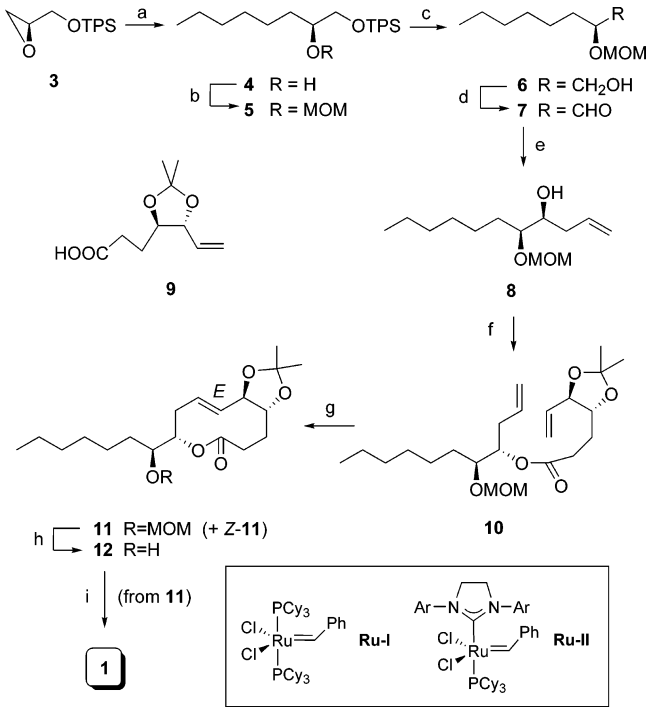
literature by up to six groups.[6] No nominal synthesis of **2** has been published so far (see below, however). In the following, we describe in full the details of the synthesis of **1** and, as well, the first synthesis of **2**.

Results and Discussion

Our retrosynthetic analysis of compound **1** (Scheme 1) relied upon the creation of the lactone ring by means of ring-closing metathesis (RCM).[7,8] Thus, sequential retrocleavage of the C=C and ester C−O bonds leads via diolefin **A** to homoallyl alcohol **B** and acid **C** (P, P′ = protecting groups), which can be derived in turn from (*R*)-glycidol and (*S,S*)-tartaric acid, respectively.

The product corresponding to intermediate **B**, homoallyl alcohol **8**, was prepared as described in Scheme 2. Commercial (*R*)-glycidol was transformed into its known[9] TPS (*tert*-butyldiphenylsilyl) ether **3**. Epoxide opening in **3** with an *n*-pentylcuprate reagent[10] afforded alcohol **4**, which was then protected as its MOM (methoxymethyl)[11] derivative **5**. Desilylation of the latter to **6** followed by Swern oxidation under mild conditions[12] afforded the α-alkoxy aldehyde (*S*)-**7**,[13] which, without purification, was immediately allowed to react with allyl tri-*n*-butyl-

SCHEME 2. Synthesis of Microcarpalide (1)[a]



[a] Reagents and conditions: (a) $CH_3(CH_2)_4MgBr$, CuI, THF, −30 °C, 87%; (b) MOMCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 18 h, 87%; (c) TBAF, THF, 5 h, room temperature, 93%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then *N,N*-diisopropylethylamine, 2 min at −78 °C, then room temperature; (e) $Bu_3SnCH_2CH{=}CH_2$, $MgBr_2{\cdot}Et_2O$, 3Å MS, CH_2Cl_2, 3 h at −78 °C, then 1.5 h at −40 °C, 60% combined yield of the two last steps; (f) **9**, DCC, DMAP, CH_2Cl_2, room temperature, 18 h, 86%; (g) 20 mol % of catalyst **Ru-I**, CH_2Cl_2, reflux, 24 h, 67:33 *E/Z* mixture (see text), 67%; (h) SMe_2, $BF_3{\cdot}Et_2O$, −10 °C, 30 min, 71%; (i) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 1 h, 66%.

stannane in the presence of $MgBr_2{\cdot}Et_2O$ (chelation control conditions).[14] This provided **8** in good yield and with high stereoselectivity (the dr value was judged to be ≥ 98%, as the minor stereoisomer was not detected by means of high-field ^1H and ^{13}C NMR). Intermediate **C** was in the present case the known acid **9**, readily prepared from (*S,S*)-tartaric acid by means of a modified literature procedure.[15]

Carboxylic acid **9** was then coupled with alcohol **8** in the presence of *N,N*′-dicyclohexylcarbodiimide (DCC)[16] to yield the diene ester **10** (Scheme 2). This reaction set the

(6) (a) Banwell, M. G.; Loong, D. T. J. *Heterocycles* **2004**, *62*, 713−734. (b) Ishigami, K.; Kitahara, T. *Heterocycles* **2004**, *63*, 785−790. (c) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V.; Karmakar, S.; Mohapatra, D. K. *ARKIVOC* **2005** (iii), 237−257. (d) Chavan, S. P.; Praveen, C. *Tetrahedron Lett*. **2005**, *46*, 1939−1941. (e) Davoli, P.; Fava, R.; Morandi, S.; Spaggiari, A.; Prati, F. *Tetrahedron* **2005**, *61*, 4427−4436. (f) Kumar, P.; Naidu, S. V. *J. Org. Chem*. **2005**, *70*, 4207−4210.

(7) (a) Fürstner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3012−3043. (b) Trnka, T.; Grubbs, R. H. *Acc. Chem.* Res. **2001**, *34*, 18−29. (c) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem*. **2001**, *46*, 181−222. (e) Love, J. A. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; pp 296−322. (f) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140.

(8) Four out of the other six syntheses of microcarpalide also make use of this type of macrocyclization. In the remaining two syntheses, the lactone ring is generated via macrolactonization.

(9) Guivisdalsky, P. N.; Bittman, R. *J. Org. Chem*. **1989**, *54*, 4637−4642. For a review on glycidol and its synthetic uses, see: Hanson, R. M. *Chem. Rev*. **1991**, *91*, 437−475.

(10) (a) Lipshutz, B. H.; Sengupta, S. *Org. React*. **1992**, *41*, 135−631. (b) Krause, N., Ed. *Modern Organocopper Chemistry*; Wiley-VCH: Weinheim, Germany, 2004.

(11) Greene, T. W.; Wuts, P. G. M., *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 27−33.

(12) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572. Racemization of the aldehyde *S*-**7** was minimized when *N,N*-diisopropylethylamine was used as the base (see: Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527−529). The ee of *S*-**7** was judged to be ≥98% in an indirect way, because no minor stereoisomers were detected by high-field NMR analysis of crude ester **10**.

(13) Both racemic and enantiomerically pure (*R*)-**7** have been previously synthesized using a different methodology based on arylthiomethyl sulfoxides. See: (a) Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem*. **1984**, *49*, 3784−3790. (b) Banfi, L.; Cabri, W.; Poli, G.; Potenza, D.; Scolastico, C. *J. Org. Chem*. **1987**, *52*, 5452−5457.

(14) For reviews on reactions with allyl tin reagents, see: (a) Nishigaichi, Y.; Takuwa, A.; Naruta, Y.; Maruyama, K. *Tetrahedron* **1993**, *49*, 7395−7426. (b) Yamamoto, Y.; Shida, N. *Adv. Detailed React. Mech*. **1994**, *3*, 1−44.

(15) Batty, D.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3193−3204. The reported overall yield was improved through modification of the described procedures (see the Supporting Information).

stage for the crucial RCM,[7] which was successful with ruthenium catalyst **Ru-I**. Thus, a 0.001 M solution of **10** and 20 mol % of **Ru-I** was heated at reflux for 24 h in dry, degassed CH_2Cl_2. This provided a 2:1 *E*/*Z* mixture of macrocyclic lactones **11**, from which the *E* isomer (depicted) was isolated by means of column chromatography on silica gel. It is worth mentioning here that the use of the second-generation ruthenium catalyst **Ru-II**[7c] gave rise almost exclusively to *Z*-**11**. Similar differences in behavior between these two catalyst types have previously been observed by other groups during the synthesis of decanolides.[17,18] These authors attributed the different stereochemical outcomes to the higher activity of the imidazolylidene-substituted catalyst, which was able to isomerize the C=C bond of the RCM product. In consequence, the *E*/*Z* ratio was no longer kinetically controlled but was, rather, the result of a chemical equilibrium. This caused a marked enhancement in the percentage of the *Z* isomer, which in their molecules was shown to be the thermodynamically more stable one. In our compounds, the same explanation is supported by theoretical calculations on lactone **11**, which show that the *Z* isomer is more stable that the *E* isomer by about 2 kcal/mol.[19]

Selective removal of the MOM group in **11** was feasible under mild conditions[20] and furnished acetonide **12**, the properties of which (NMR, MS) were identical with those reported.[2] Preparation of the target molecule **1** was finally achieved by one-pot removal of all protecting groups in compound **11**.[21] The physical and spectral properties of synthetic **1** turned out to be identical with those reported for the natural compound. As reported by Hemscheidt and co-workers for the natural product,[2] the NMR spectra of synthetic **1** at room temperature revealed the presence of two slowly interconverting conformers in an approximate (3−3.5):1 ratio.

The isolation and structure elucidation of lethaloxin was reported in 1993, and its *relative* configuration was proposed to be **2**.[3] The compound was not mentioned again in the literature until 2002, when Fürstner and co-workers[17a] disclosed the synthesis of the structurally related decanolides herbarumins I (**13**) and II (**14**) (Figure 2) and cleared by synthetic methods the stereochemical puzzle around pinolidoxin, a further decanolide of the same structural type. This compound, however, was represented in that paper with the structure and absolute configuration **2**. Furthermore, these authors depicted the structure and relative configuration of lethaloxin as **15**, which is not the previously reported structure.[3,22] Adding more matter to this confusion, the structure of lethaloxin was depicted as **16** in a later publication of Ley and coworkers, who described there their own synthesis of **14**.[23] These inconsistencies led us to undertake our own synthesis of lethaloxin. An added element of interest in the present case is given by the interesting pharmacological properties of members of this compound class.[1] In addition, lactones of this type have also been found to exhibit marked phytotoxicity, which has been related to its inhibitory activity on phenylalanine ammonia lyase, a key plant enzyme involved in the biosynthesis of phenylpropanoids.[24] This feature renders these lactones promising lead structures for the search of novel herbicides. Furthermore, lactones **13** and **14** have recently been found to inhibit the activation of the calmodulin-dependent enzyme cAMP phosphodiesterase, a property which might endow them with agrochemical and medicinal interest.[25] As shown in the following, we have found that the structure and absolute configuration of natural (+)-lethaloxin is represented by the structural formula **2** *and is therefore identical with natural (+)-pinolidoxin*.[26]

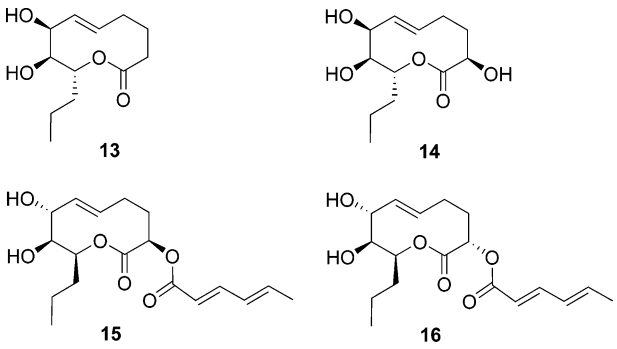


FIGURE 2. Structures of herbarumin I (**13**), herbarumin II (**14**) and two stereoisomers (**15**, **16**) of lethaloxin (pinolidoxin).

Our approach to the lethaloxin framework (Scheme 3; P, P′ = protecting groups) was based on the same concept used in the microcarpalide synthesis and relied again on the formation of the lactone ring via RCM. Thus, retrocleavage of the C=C bond and of the sorboyl ester moiety

(16) (a) Mikołajczyk, M.; Kiełbasiński, P. *Tetrahedron* **1981**, *37*, 233−284. (b) Mulzer, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 6, pp 323−380.

(17) (a) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem.* Soc. **2002**, *124*, 7061−7069. These authors used a ruthenium catalyst structurally similar to **A** but having an indenylidene group instead of the benzylidene moiety. The other catalyst was close to **B** but with an additional C=C bond in the imidazole ring. (b) Liu, D.; Kozmin, S. A. *Org. Lett*. **2002**, *4*, 3005−3007. (c) For the creation of medium-sized and large rings via RCM, see pertinent citations in ref 17a and: Prunet, J. *Angew. Chem., Int. Ed*. **2003**, *42*, 2826−2830.

(18) Responsible for this and related nonmetathetic processes may be ruthenium hydride intermediates, the formation of which has recently been demonstrated in the case of **Ru-II**: Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc*. **2004**, *126*, 7414−7415. It is also worth mentioning that, although more rarely, the catalyst **Ru-I** has also been found to induce *E*−*Z* isomerizations: Kalesse, M.; Quitschalle, M.; Claus, M.; Gerlach, K.; Pahl, A.; Meyer, H. H. *Eur. J. Org. Chem*. **1999**, 2817−2823.

(19) Theoretical calculations were first performed at the semiempirical level (AM1) and gave a difference in energy contents of 2 kcal/mol between both stereoisomers. When the calculations were made with ab initio methods (HF/3-21G), the difference turned out to be 1.9 kcal/mol.

(20) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem*. **1995**, *60*, 4419−4427. See also: Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull*. **1980**, *28*, 3662−3664.

(21) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1997**, *62*, 377−386.

(22) To the best of our knowledge, no structural revision of lethaloxin has appeared in the literature since the initial report of 1993.

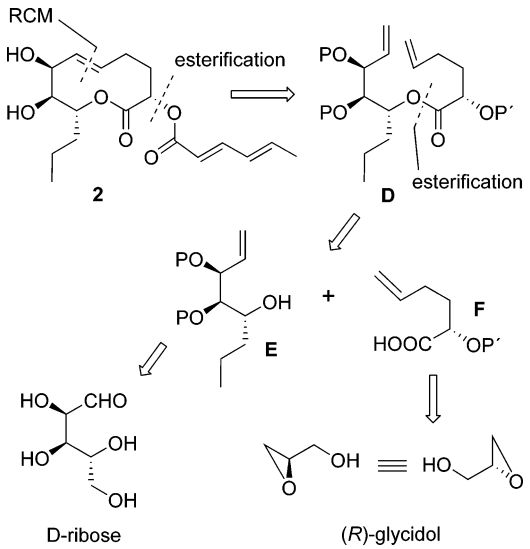
(23) Díez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodríguez, F. *Helv. Chim. Acta* **2003**, *86*, 3717−3729. In this paper, the stereostructure of pinolidoxin has also been erroneously depicted.

(24) (a) Vurro, M.; Ellis, B. E. *Plant Sci.* **1997**, *126*, 29−38. (b) Evidente, A.; Capasso, R.; Andolfi, A.; Vurro, M.; Zonno, M.-C. *Nat. Toxins* **1998**, *6*, 183−188. (c) Zonno, M.-C.; Vurro, M. *Weed Res.* **1999**, *39*, 15−20.

(25) Rivero-Cruz, J. F.; Macías, M.; Cerda-García-Rojas, C.; Mata, R. *J. Nat. Prod*. **2003**, *66*, 511−514.

(26) For a synthesis of the non-natural enantiomer of pinolidoxin, see ref 17b.

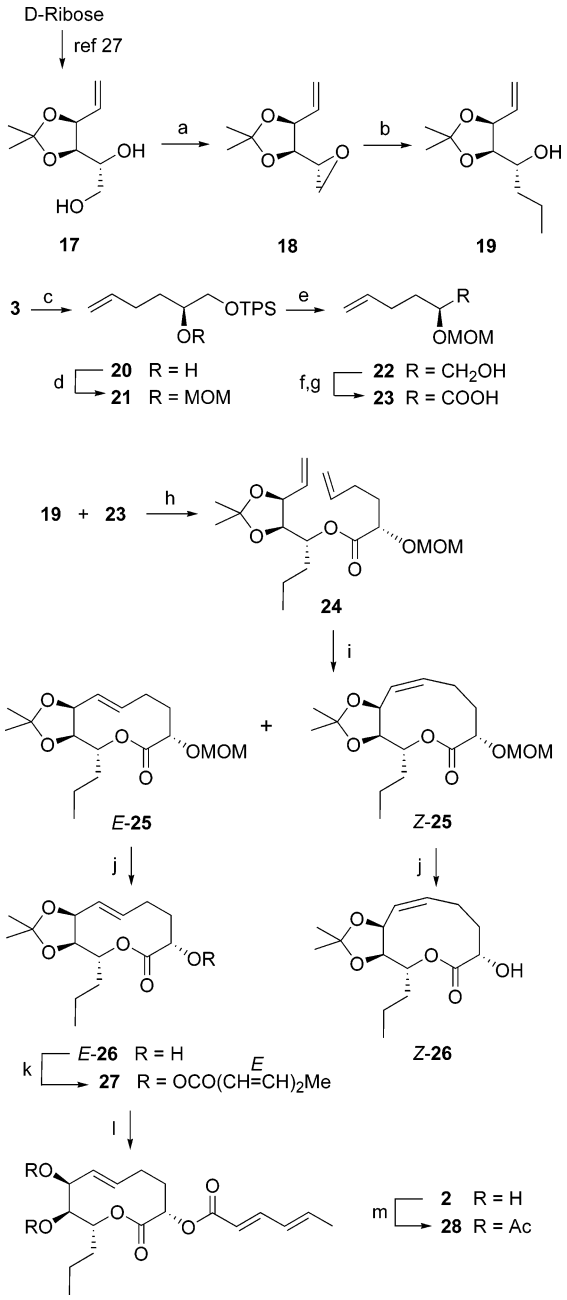
SCHEME 3. Retrosynthetic Plan for Lethaloxin (2)



gives diolefin **D**. Further cleavage of the ester function generates alcohol **E** and acid **F**. Since the former has the same absolute configuration in its triol fragment as D-ribose, this commercially available sugar was chosen as the chiral precursor. Acid **F** can be obtained from (*R*)-glycidol in a way similar to that followed in the synthesis of microcarpalide (Scheme 2).

The specific details of the synthesis are depicted in Scheme 4. D-Ribose was converted in two steps into diol **17** as described.[27] Diol **17** was then dehydrated to epoxide **18** by means of the Mitsunobu reaction.[28] Epoxide ring opening in **18** was performed with an ethylcuprate reagent[9] and yielded alcohol **19** in 48% overall yield from D-ribose acetonide.[29] Furthermore, epoxide **3** was treated as described[30] with an allylcuprate reagent to afford alcohol **20**, which was then protected as its MOM derivative **21**. Desilylation and sequential two-step oxidation furnished acid **23**,[31] which was coupled with alcohol **19** using the Yamaguchi procedure.[32] This provided ester **24**, which was subjected to RCM in the presence of catalyst **Ru-I**. As in the synthesis of microcarpalide, an *E*/*Z* mixture of cyclic olefins **25** was formed in 74% overall yield (ratio of geometric isomers 76:24, with the *E* isomer predominating). Both stereoisomers were separated by column chromatography and identified by their spectral features.[33,34] Compound *E*-**25** was subjected to selective deprotection[20] of the MOM group to yield hydroxy lactone *E*-**26**,[35] which was then esterified with sorbic acid using again the Yamaguchi procedure. The resulting ester **27**[35] was subjected to cleavage of the acetonide moiety[21] to provide the dihydroxy lactone **2**,

SCHEME 4. Synthesis of (+)-Lethaloxin (2)[a]



[a] Reagents and conditions: (a) PPh_3, diisopropyl azodicarboxylate, $CHCl_3$, reflux, overnight; (b) EtMgBr, CuI, THF, −30 °C, 55% overall from **17**; (c) ref 30; (d) MOMCl, *N*,*N*-diisopropylethylamine, CH_2Cl_2, room temperature, 18 h, 88%; (e) TBAF, THF, 5 h, room temperature, 95%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then *N*,*N*-diisopropylethylamine, 2 min at −78 °C, then 0 °C; (g) $NaClO_2$, NaH_2PO_4, aqueous *t*BuOH; (h) 2,4,6-trichlorobenzoyl chloride, *N*,*N*-diisopropylethylamine, DMAP, THF, room temperature, overnight, 96%; (i) 20% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, 6 h, Δ, 74%, 76:24 *E*/*Z* mixture (see text); (j) SMe_2, $BF_3{\cdot}Et_2O$, −10 °C, 30 min, 69%; (k) sorbic acid, 2,4,6-trichlorobenzoyl chloride, *N*,*N*-diisopropylethylamine, DMAP, THF, room temperature, overnight, 67%; (l) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 1 h, 81%. (m) Ac_2O, pyridine, room temperature, 77%.

which proved identical with natural (+)-lethaloxin in its optical rotation and spectral features[3] (see the Supporting Information). *These physical and spectral data were also identical with those reported for both natural*[36] *and synthetic*[17a] *(+)-pinolidoxin*. This is also the case for the

(27) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1189−1193.

(28) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Hughes, D. L. *Org. React*. **1992**, *42*, 335−656. (c) Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, 317−334.

(29) Alcohol **19** has also been prepared by Fürstner and co-workers[17a] from the highly expensive D-ribonolactone.

(30) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Chem. Eur. J*. **2002**, *8*, 1621−1636.

(31) The enantiomer of acid **23** has been reported by Fürstner and co-workers.[17a]

(32) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989−1993.

corresponding diacetates. These two natural decanolides therefore are identical.

Concluding Remarks

In summary, convergent, stereoselective syntheses of the pharmacologically active lactones **1** and **2** have been achieved from the commercially available, chiral reagents (*R*)-glycidol, (*S,S*)-tartaric acid, and D-ribose as the starting materials. Since both enantiomers of these chiral starting materials are available, our synthesis is adaptable to the preparation of not only the natural products themselves but also of enantiomers, diastereoisomers, and further analogues thereof. All of these derivatives will be useful for future pharmacological structure−activity relationships. In addition, our syntheses have served to establish the absolute configuration of natural (+)-lethaloxin and to show its identity with (+)-pinolidoxin.

Experimental Section

General Features. These are described in detail in the Supporting Information.

Ester 10. Acid **9** (1.5 mmol in crude form, see the preparation in the Supporting Information), alcohol **8** (230 mg, 1 mmol), and DMAP (6 mg, 0.05 mmol) were dissolved in dry CH_2Cl_2 (6 mL) and treated with a solution of DCC (310 mg, 1.5 mmol) in dry CH_2Cl_2 (6 mL). The reaction mixture was then stirred at room temperature for 18 h, diluted with CH_2Cl_2 (10 mL), and filtered to eliminate the solid *N*,*N*′-dicyclohexylurea. Solvent removal gave a residue, which was dissolved in Et_2O (40 mL) and worked up. Solvent removal and column chromatography on silica gel (hexanes−EtOAc, 9:1) provided ester **10** (355 mg, 86% based on **8**): oil; $[\alpha]_D$ = +4.2° (*c* 1; $CHCl_3$); IR ν_{max} 1738 (ester C=O) cm^{-1}; ^1H NMR (500 MHz) δ 5.80−5.70 (2H, m), 5.36 (1H, br d, *J* = 17.2 Hz), 5.24 (1H, br d, *J* = 10.4 Hz), 5.10−5.00 (3H, m), 4.69 (1H, d, *J* = 7 Hz), 4.67 (1H, d, *J* = 7 Hz), 3.98 (1H, t, *J* = 7.8 Hz), 3.69 (1H, dt, *J* = 8.3, 3.5 Hz), 3.58 (1H, m), 3.39 (3H, s), 2.55−2.40 (3H, m), 2.33 (1H, m), 1.95 (1H, m), 1.82 (1H, m), 1.50 (2H, m), 1.40 (3H, s), 1.38 (3H, s), 1.40−1.25 (8H, br m), 0.87 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz) δ 172.5, 108.8 (C), 135.1, 133.9, 82.4, 79.5, 78.0, 73.7 (CH), 119.0, 117.7, 96.7, 34.7, 31.7, 30.7, 30.5, 29.4, 26.9, 25.3, 22.6 (CH_2), 55.9, 27.2, 26.9, 14.0 (CH_3); HR EIMS *m/z* (relative intensity) 412.2834 (M^+, 1), 397 (11), 229 (58), 125 (100), 98 (64), calcd for $C_{23}H_{40}O_6$ 412.2825. For the graphical NMR spectra of **10**, see the Supporting Information in ref 5.

Lactones 11. Diolefin **10** (330 mg, 0.8 mmol) was dissolved in dry, degassed CH_2Cl_2 (20 mL) and added dropwise within 1 h to a refluxing solution of ruthenium catalyst **Ru-I** (131 mg, 0.16 mmol) in dry, degassed CH_2Cl_2 (780 mL). The reaction mixture was heated at reflux until consumption of the starting material (20−24 h, TLC monitoring). Solvent removal in vacuo and column chromatography of the residue on silica gel (hexanes−EtOAc, 9:1) first furnished (*E*)-**11** (139 mg, 45%) and then (*Z*)-**11** (67 mg, 22%). When the same reaction was performed in the presence of ruthenium catalyst **Ru-II** (reaction time 1 h), lactone (*Z*)-**11** was obtained as the sole stereoisomer in 73% yield. Physical and spectral data of (*E*)-**11**: oil; $[\alpha]_D$ = −18.1° (*c* 0.6; $CHCl_3$); IR ν_{max} 1733 (lactone C=O) cm^{-1}; ^1H NMR (500 MHz) δ 5.75 (1H, m), 5.34 (1H, dd, *J* = 15.5, 9 Hz), 4.92 (1H, m), 4.70 (1H, d, *J* = 7 Hz), 4.68 (1H, d, *J* = 7 Hz), 3.93 (1H, t, *J* = 9 Hz), 3.70−3.60 (2H, m), 3.40 (3H, s), 2.70−2.60 (1H, m), 2.54 (1H, dt, *J* = 13.3, 4.5 Hz), 2.44 (1H, m), 2.40−2.30 (2H, m), 2.10 (1H, m), 2.00 (1H, m), 1.41 (6H, s), 1.40−1.20 (9H, br m), 0.88 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz) δ 171.8, 108.8 (C), 130.2, 129.4, 84.4, 79.8, 79.3, 73.6 (CH), 96.5, 34.3, 31.8, 30.8, 30.5, 29.4, 25.5, 25.4, 22.6 (CH_2), 56.1, 27.2, 27.0, 14.1 (CH_3); HR CIMS *m/z* (relative intensity) 385.2600 (M + H^+, 8), 369 (25), 353 (11), 327 (42), 295 (84), 265 (80), 220 (25), 157 (100), calcd for $C_{21}H_{37}O_6$ 385.2590. For the graphical NMR spectra of (*E*)-**11**, see the Supporting Information in ref 5. For the physical and spectral data of (*Z*)-**11**, see the Supporting Information of this paper.

Lactone 12. Lactone (*E*)-**11** (25 mg, 0.065 mmol) was dissolved in dimethyl sulfide (2 mL), and the solution was cooled to −10 °C and treated with $BF_3{\cdot}Et_2O$ (82 μL, 0.65 mmol). The reaction mixture was stirred at the same temperature for 30 min. Workup (CH_2Cl_2) and column chromatography on silica gel (hexanes−EtOAc, 1:1) yielded **12** (16 mg, 71%): oil; $[\alpha]_D$ = −27.3° (*c* 0.4; $CHCl_3$); IR ν_{max} 3270 (br, OH), 1719 (lactone C=O) cm^{-1}; NMR data identical with those reported;[2] HR EIMS *m/z* (relative intensity) 340.2256 (M^+, 2), 325 (M^+−Me, 26), 238 (22), 180 (100), 123 (82), 110 (84), 85 (56), 70 (58), calcd for $C_{19}H_{32}O_5$ 340.2249. For the graphical NMR spectra of **12**, see the Supporting Information in ref 5.

Microcarpalide (1). An ice-cooled solution of lactone (*E*)-**11** (77 mg, 0.2 mmol) in dry CH_2Cl_2 (5 mL) was treated with ethanedithiol (65 μL, 0.8 mmol) and $BF_3{\cdot}Et_2O$ (50 μL, 0.4 mmol). The reaction mixture was stirred at 0 °C for 1 h. Workup (EtOAc) and column chromatography on silica gel (hexanes−EtOAc, 1:1) afforded **1** (40 mg, 66%): oil; $[\alpha]_D$ = −20.2° (*c* 0.4; MeOH), lit. $[\alpha]_D$ = −22° (*c* 0.67; MeOH); IR ν_{max} 3400 (br, OH), 1724 (lactone C=O) cm^{-1}; NMR data identical with those reported.[2] For the graphical NMR spectra of synthetic **1**, see the Supporting Information in ref 5.

Ester 24. Acid **23** (2 mmol in crude form; see the preparation in the Supporting Information), alcohol **19** (200 mg, 1 mmol), *N*,*N*-diisopropylethylamine (435 μL, 2.5 mmol), and DMAP (6 mg, 0.05 mmol) were dissolved in dry THF (35 mL) and treated with 2,4,6-trichlorobenzoyl chloride (312 μL, 2 mmol). The reaction mixture was then stirred overnight at room temperature. Workup (Et_2O) and column chromatography on silica gel (hexanes−EtOAc, 7:3) furnished ester **24** (342 mg, 96% based on **19**): oil; $[\alpha]_D$ = −24.6° (*c* 2.1, $CHCl_3$); IR ν_{max} 1752 (ester C=O) cm^{-1}; ^1H NMR δ 5.85−5.75 (2H, m), 5.35 (1H, br d, *J* = 17.3 Hz), 5.22 (1H, br d, *J* = 10.3 Hz), 5.04 (1H, dq, *J* = 17, 1.5 Hz), 5.00 (1H, overlapped m), 4.98 (1H, dt, *J* = 7.6, 3.5 Hz), 4.67 (1H, d, *J* = 6.8 Hz), 4.63 (1H, d, *J* = 6.8 Hz), 4.60 (1H, br t, *J* = 6.5 Hz), 4.19 (1H, dd, *J* = 7.6, 6.5 Hz), 4.08 (1H, dd, *J* = 7.8, 4.7 Hz), 3.39 (3H, s), 2.20 (2H, m), 1.90−1.80 (2H, m), 1.70−1.60 (2H, m), 1.47 (3H, s), 1.36 (3H, s), 1.40−1.25 (2H, m), 0.91 (3H, t, *J* = 7.3 Hz); ^{13}C NMR δ 171.5, 108.8 (C), 137.3, 133.1, 78.8, 78.1, 74.4, 72.3 (CH), 118.7, 115.5, 96.0, 33.4, 32.1, 29.4, 17.8 (CH_2), 56.0, 27.6, 25.3, 14.0 (CH_3); HR EIMS *m/z* (relative intensity) 341.1940 (M^+ − Me, 12), 127 (34), 98 (100), calcd for $C_{19}H_{32}O_6$ − Me 341.1964.

Lactones 25. Diolefin **24** (285 mg, 0.8 mmol) was dissolved in dry, degassed CH_2Cl_2 (20 mL) and added dropwise within

(33) After selective cleavage of the MOM group in olefin *Z*-**25**, the crystalline hydroxy lactone *Z*-**26** was formed. The structure and absolute configuration of *Z*-**26** were confirmed by means of an X-ray diffraction analysis. Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Center as Supporting Information with reference CCDC-271535. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, +44(0)-1223−336033; e-mail, deposit@ccdc.cam.ac.uk).

(34) As in the case of microcarpalide, the catalyst **Ru-II** provided only the undesired *Z*-**25**. Again, the preferential formation of the more stable *Z* isomer is due to thermodynamic control of the RCM process by the catalyst **Ru-II**. It is worth mentioning, however, that, with appropriately allocated substituents in the 10-membered ring, the *E* isomer may become the more stable from the thermodynamic point of view and thus favored in the RCM process, even with catalyst **Ru-II**.[23]

(35) Lactones *E*-**26** and **27** correspond to compounds **24** and **45** in ref 17a, but the physical and spectral data of the last two compounds are not given in the Supporting Information of that paper. The physical and spectral data of the enantiomer of **45** (named **43** there) are given, however.

(36) Evidente, A.; Lanzetta, R.; Capasso, R.; Vurro, M.; Bottalico, A. *Phytochemistry* **1993**, *34*, 999−1003.

1 h to a refluxing solution of ruthenium catalyst **Ru-I** (131 mg, 0.16 mmol) in dry, degassed CH_2Cl_2 (780 mL). The reaction mixture was heated at reflux until consumption of the starting material (4−6 h, TLC monitoring). Solvent removal in vacuo and column chromatography of the residue on silica gel (hexanes−EtOAc, 9:1) provided first *E*-**25** (150 mg, 57%) and then *Z*-**25** (47 mg, 18%). When the same reaction was performed in the presence of ruthenium catalyst **Ru-II** (reaction time, 2 h), lactone *Z*-**25** was obtained as the sole stereoisomer in 72% yield. Physical and spectral data of (*E*)-**25**: oil; $[\alpha]_D = +30.2°$ (*c* 1, $CHCl_3$); IR ν_{max} 1730 (lactone C=O) cm^{-1}. The ^1H NMR spectrum shows the presence of two slowly interconverting conformers in an approximate 2.5 to 3:1 relation, which give rise to two sets of partly overlapped signals (the visible signals of the minor conformer with relative proton intensities are given in italics). The ^{13}C NMR spectrum also shows two sets of signals (signals of the minor conformer are given in italics): ^1H NMR δ 5.84 (1H, dd, J = 15.6, 3.3 Hz), 5.63 (1H, m), *5.49 (1H, br dd, J = 16.5, 8 Hz)*, 4.98 (1H, ddd, J = 10, 9, 3 Hz), *4.79 (1H, br t, J = 9 Hz)*, *4.73 (1H, br t, J = 7.3 Hz)*, 4.68 (2H, s), 4.66 (1H, m), 4.29 (1H, br d, J = 5.5 Hz), *4.17 (2H, m)*, 4.00 (1H, dd, J = 10, 4.6 Hz), 3.39 (3H, s), *3.33 (3H, s)*, 2.40 (1H, m), *2.30 (1H, m)*, *2.20 (1H, m)*, 2.20−2.05 (2H, m), 2.00 (1H, m), 1.80 (2H, m), *1.65 (1H, m)*, 1.51 (3H, s), *1.44 (3H, s)*, 1.36 (3H, s), *1.33 (3H, s)*, 1.35−1.25 (2H, m), 0.91 (3H, t, J = 7 Hz); ^{13}C NMR δ 174.4, *172.4*, 109.1, *108.9* (C), *131.7*, 128.6, *128.0*, 123.2, *78.2, 78.1*, 78.0, 76.2, *75.7*, 73.3, 71.4 (CH), *95.9*, 95.7, 34.2, *33.8*, 31.9, *30.3*, 27.2, *26.0*, *18.1*, 17.8 (CH_2), *55.8*, 55.7, 28.5, *27.9*, 26.2, *25.2*, 13.9, *13.8* (CH_3); HR EIMS *m/z* 328.1843 (M^+, 1), 283 (18), 171 (66), 111 (100), calcd for $C_{17}H_{28}O_6$ 328.1885. For the physical and spectral data of *Z*-**25**, see the Supporting Information of this paper.

Lactone (*E*)-**26**. Lactone (*E*)-**25** (132 mg, 0.4 mmol) was dissolved in dimethyl sulfide (12 mL), cooled to −10 °C, and treated with $BF_3{\cdot}Et_2O$ (0.5 mL, ca. 4 mmol). The reaction mixture was stirred at the same temperature for 30 min. Workup (CH_2Cl_2) and column chromatography on silica gel (hexanes−EtOAc, 7:3) yielded *E*-**26** (78 mg, 68%): oil; $[\alpha]_D$ +81.4° (*c* 1.8, $CHCl_3$); IR ν_{max} 3480 (br, OH), 1728 (lactone C=O) cm^{-1}. The ^1H NMR spectrum shows the presence of two slowly interconverting conformers in an approximate 2.5 to 3:1 relation, which give rise to two sets of partly overlapped signals (the visible signals of the minor conformer with relative proton intensities are given in italics). The ^{13}C NMR spectrum also shows two sets of signals (signals for the minor conformer are given in italics): ^1H NMR δ 5.79 (1H, dd, J = 15.7, 3.3 Hz), *5.74 (1H, overlapped m)*, 5.66 (1H, br ddd, J = 15.7, 11.5, 4.2 Hz), *5.53 (1H, br dd, J = 16.3, 8.4 Hz)*, 5.03 (1H, ddd, J = 10, 9, 2.7 Hz), *4.70 (2H, m)*, 4.64 (1H, br s), 4.39 (1H, br d, J = 5.5 Hz), *4.30 (1H, m)*, *4.20 (1H, dd, J = 9.8, 6.6 Hz)*, 3.98 (1H, dd, J = 10, 4.7 Hz), 2.50−2.45 (1H, m), 2.40 (1H, br s, OH), 2.20−2.10 (2H, m), 2.00 (1H, m), 1.80 (1H, m), *1.65 (1H, m)*, 1.60−1.50 (1H, m), 1.54 (3H, s), *1.44 (3H, s)*, 1.36 (3H, s), 1.40−1.30 (2H, m), *1.33 (3H, s)*, 0.91 (3H, t, J = 7.2 Hz); ^{13}C NMR δ 174.3, 109.2, *109.0* (C), *131.1, 129.5*, 127.8, 124.6, *78.1, 77.9*, 77.8, 76.0, 71.9, *70.3*, 70.2 (CH), 34.2, *33.9*, 32.4, *32.2*, 27.0, *18.2*, 17.9 (CH_2), 28.5, *27.8*, 26.2, *25.1, 25.0*, 13.8 (CH_3); HR EIMS *m/z* (relative intensity) 284.1693 (M^+, 14), 269 (36), 241 (34), 115 (100), calcd for $C_{15}H_{24}O_5$ 284.1623.

Lactone 27. Lactone *E*-**26** (71 mg, 0.25 mmol), *N*,*N*-diisopropylethylamine (110 μL, ca. 0.6 mmol), DMAP (6 mg, 0.05 mmol), and sorbic acid (56 mg, 0.5 mmol) were sequentially dissolved in dry THF (10 mL) and treated with 2,4,6-trichlorobenzoyl chloride (80 μL, ca. 0.5 mmol). The reaction mixture was then stirred overnight at room temperature. Workup (Et_2O) and column chromatography on silica gel (hexanes−EtOAc, 9:1) furnished lactone **27** (63 mg, 67%, 86% based on recovered starting material), together with unreacted (*E*)-**26** (16 mg): oil; $[\alpha]_D = +145.5°$ (*c* 1, $CHCl_3$), lit.[17a] for the enantiomer $[\alpha]_D = -158.9°$ (*c* 0.54, CH_2Cl_2); IR ν_{max} 1721 (br, lactone and ester C=O) cm^{-1}; the NMR spectra, which show the presence of two conformers, are essentially identical with those reported;[17a] HR EIMS *m/z* (relative intensity) 378.2061 (M^+, 2), 320 (11), 283 (18), 235 (11), 110 (66), 83 (77), 95 (100), calcd for $C_{21}H_{30}O_6$ 378.2042.

Lethaloxin (2). An ice-cooled solution of lactone **27** (57 mg, 0.15 mmol) in dry CH_2Cl_2 (4 mL) was treated with ethanedithiol (25 μL, 0.3 mmol) and $BF_3{\cdot}Et_2O$ (20 μL, ca. 0.15 mmol). The reaction mixture was stirred at 0 °C for 1 h. Workup (EtOAc) and column chromatography on silica gel (hexanes−EtOAc, 1:1) afforded **2** (41 mg, 81%): oil; $[\alpha]_D = +126.7°$ (*c* 0.25, $CHCl_3$), lit.[3] for natural (+)-lethaloxin $[\alpha]_D = +129°$ (*c* 0.2, $CHCl_3$), lit.[36] for natural (+)-pinolidoxin, $[\alpha]_D = +142.9°$ (*c* 0.31, $CHCl_3$), lit.[17a] for synthetic (+)-pinolidoxin, $[\alpha]_D = +143.2°$ (*c* 0.25, $CHCl_3$), lit.[17a] for synthetic (−)-pinolidoxin, $[\alpha]_D = -114.4°$ (*c* 0.54, CH_2Cl_2), lit.[17b] for synthetic (−)-pinolidoxin, $[\alpha]_D = -140°$ (*c* 0.2, $CHCl_3$); IR ν_{max} 3480 (br, OH), 1719 (br, lactone and ester C=O) cm^{-1}; the NMR spectra, which show the presence of only one conformer, are essentially identical with those of natural lethaloxin (NMR spectra of the natural sample were available) and, as well, with those of either natural or synthetic pinolidoxin (see Tables 1 and 2 in the Supporting Information); HR EIMS *m/z* (relative intensity) 338.1745 (M^+, 1), 253 (2), 141 (8), 95 (100), 67 (22), calcd for $C_{18}H_{26}O_6$ 338.1729.

Acknowledgment. Financial support has been granted by the Spanish Ministry of Education and Science (Project BQU2002-00468) and by the AVCyT (Projects GRUPOS03/180 and GV05/52). J.M. thanks the Spanish Ministry of Education and Science for a contract of the Ramón y Cajal program. J.G.-F. thanks the Spanish Ministry of Education and Science for a predoctoral fellowship (FPU program). We further thank Prof. G. Nasini, from the Dipartimento di Chimica, Materiali ed Ingegneria Chimica "Giulio Natta", Politecnico di Milano, Milano, Italy, for sending us NMR spectra of natural lethaloxin.

Supporting Information Available: Text giving a description of general spectroscopic features and several experimental procedures, tables giving physical and spectral data of synthetic compounds **4**−**6**, **8**, *Z*-**11**, **21**, **22**, *Z*-**25,** and *Z*-**26**, a comparison of ^1H and ^{13}C NMR data of **2** with those of natural lethaloxin and both natural and synthetic pinolidoxin, and a comparison of ^1H NMR data of the diacetate of **2** (**28**) with those of the diacetates of natural lethaloxin and natural pinolidoxin, figures giving graphical NMR spectra of compounds **2**, **4**−**6**, **8**, **10**, *E*-**11**, *Z*-**11**, **12**, **21**, **22,** and **24**−**28**, and a CIF file giving crystallographic data of compound (*Z*)-**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051353P